menthol (*cis*-*p*-menthan-*trans*-2-ol). This material is identified as 1(7)-*p*-menthen-*trans*-2-ol (VI) which would be expected to yield these carvomenthols.

trans-**Carvotanacetol (VII)**.—The material obtained from the fraction boiling at 89.2° (4 mm.) had the following properties: d^{25}_4 0.9215, $n^{25}D$ 1.4757, and $[\alpha]D$ −113.9° (*c* 4.1, ethanol). Its infrared spectrum shows strong absorption at 3.03 and 9.56 to 9.7 μ indicating a secondary alcohol, and at 12.43 μ indicating a trisubstituted double bond.[17] Catalytic reduction (PtO_2) yields a mixture giving two major g.l.c. peaks which correspond to those of neo- and isocarvomenthol with the former being the major component. These products and the infrared spectrum are those predicted for 1-*p*-menthen-*trans*-6-ol (*trans*-carvotanacetol) (VII). Jefferies and Milligan[23] give the properties of *dl*-*trans*-carvotanacetol as d_{20} 0.9290 and $n^{20}D$ 1.4786.

1(7)-*p*-Menthen-*cis*-2-ol (VIII). This material, the major component of the fraction boiling at 78° (2 mm.), had the following properties: d^{25}_4 0.9262, $n^{25}D$ 1.4803, and $[\alpha]D$ +8.5° (*c* 8.25, ethanol). Its infrared spectrum shows strong absorption at 3.02 μ and in the 9.2 to 9.5 μ region indicating a secondary alcohol, and at 3.27, 6.05, 11.2 and 11.5 μ indicating an unsymmetrically disubstituted double bond.[17] Catalytic reduction (PtO_2) yields a mixture giving two major g.l.c. peaks corresponding to carvomenthol (*trans*-*p*-menthan-*cis*-2-ol) and neoisocarvomenthol (*cis*-*p*-menthan-*cis*-2-ol), the latter being the major component. These data are that predicted for 1(7)-*p*-menthen-*cis*-2-ol (VIII).

Preparation of the Carvomenthols.—Carvomenthol was obtained by g.l.c. purification of the products obtained by the anti-Markovnikov hydration of carvomenthene effected by the procedure by Brown.[24] Isocarvomenthol was obtained similarly from the catalytic reduction (PtO_2–HOAc) of isodihydrocarveol. Neo- and neoisocarvomenthols were obtained similarly from the products of the catalytic reduction (PtO_2–HOAc) of carvomenthone. The physical properties of the carvomenthols are given in Table III. The optical rotations were determined in ethanol at concentrations ranging from 3 to 10%.

TABLE III

PROPERTIES OF THE CARVOMENTHOLS

Compound	d^{25}_4		$n^{25}D$		$[\alpha]D$	
Carvomenthol	0.891	0.896[a]	1.4597	1.4595[a]	−21°	+26°[a]
Neocarvomenthol	.899	.897[a]	1.4611	1.4610[a]	+30°	−42°[a]
Isocarvomenthol	.906	.907[a]	1.4634	1.4640[a]	+16°	−18°[a]
Neoisocarvomenthol	.911	.908[a]	1.4652	1.4654[a]	+32°	−35°[a]

[a] R. G. Johnson and J. Read, *J. Chem. Soc.*, 1139 (1935). Original values were recalculated to 25°.

Acknowledgment.—The authors wish to express their appreciation to H. E. McLaughlin, Newport Industries, for supplying the carvomenthene used in this work; to Dr. J. P. Bain, The Glidden Company, for various reference compounds; and to Dr. J. C. Braun of this laboratory, for the reference sample of carvomenthol.

(23) P. R. Jefferies and B. Milligan, *J. Chem. Soc.*, 4348 (1956).

(24) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **81**, 6423 (1959).

Stereoisomerism. I. The Synthesis of Some *cis*- and *trans*-1,3-Cyclohexanedialkanoic Acids. The Assignment of Configuration by Nuclear Magnetic Resonance[1]

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The *cis*- and *trans*-1,3-cyclohexanediacetic and dipropionic acids were prepared by consecutive Arndt–Eistert homologation of the isomeric 1,3-cyclohexanedicarboxylic acids. The 1,3-cyclohexanedipropionic acids were also prepared by double addition of ethyl acrylate to the piperidine enamine of cyclohexanone, followed by Wolff–Kishner reduction of the intermediate keto diester. The major product isolated from this reduction was the *trans*-1,3-cyclohexanedipropionic acid. The nuclear magnetic resonance spectra of these isomeric diacids allow assignment of *cis* or *trans* configuration.

There are numerous reported studies on the stereochemistry of various substituted cyclic systems. However, for the most part, these studies have been devoted to considerations of alkylated cyclic systems or where functional groups are attached directly to the ring.[2] In connection with studies devoted to the stereochemistry of cyclic systems, where functional groups are attached to alkyl side chains, it was necessary to prepare a series of such isomeric derivatives and to be able to assign configurations readily to these types of systems. This paper reports the synthesis of the *cis*- and *trans*-1,3-cyclohexanediacetic and dipropionic acids and an examination of their nuclear magnetic resonance spectra.

A relatively straightforward approach to the synthesis of these compounds was the Arndt–Eistert homologation of the known and readily available *cis*- and *trans*-1,3-cyclohexanedicarboxylic acids (**1** and **2**).[3] This route appeared particularly attractive in view of the reported stereospecificity of this reaction with the corresponding half esters.[4]

Using the Newman–Beal modification of the Arndt–Eistert reaction (silver benzoate–triethylamine in absolute methanol),[5] the *cis*- and *trans*-1,3-cyclohexanedicarboxylic acids (**1** and **2**) were converted to the corresponding *cis*- and *trans*-1,3-cyclohexanediacetic acids (**3** and **4**), m.p. 138–139° and 118–119°, respectively, in 55 and 30% yields. Similarly, homologation of the diacetic acids gave the *cis*- and *trans*-1,3-cyclohexanedipropionic acids (**5** and **6**), m.p. 97–98° and 94–95°, respectively, in 55 and 21% yields. The homologation reactions in the *cis* series utilized N,N′-dinitroso-N,N′-dimethylterephthalamide (Du Pont EXR-101) as diazomethane precursor, while those in the *trans* series utilized *p*-tolylsulfonylmethylnitrosoamide. The dif-

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) For general references to these studies, *cf.* E. L. Eliel, "The Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(3) A. Skita and R. Rossler, *Chem. Ber.*, **72B**, 265 (1939).

(4) F. Ramirez and J. W. Sargent, *J. Am. Chem. Soc.*, **74**, 5785 (1952).

(5) M. S. Newman and D. F. Beal, *ibid.*, **72**, 5163 (1950).

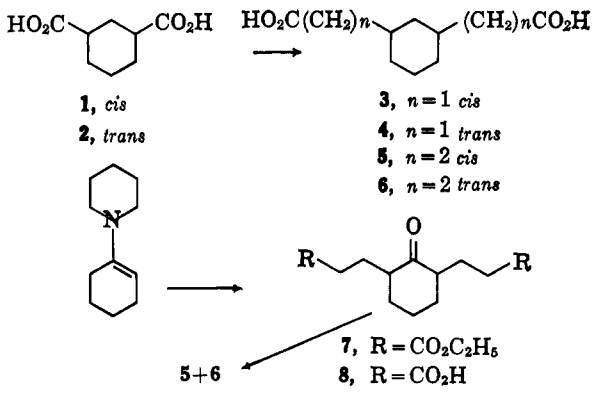
ferences in yields of homologated products when using *p*-tolylsulfonylmethylnitrosamide and Du Pont EXR-101 are probably due to a more efficient generation of diazomethane using the latter reagent (see Experimental). The low yields of all these homologated products may be attributed, at least in part, to the formation of polymeric material during the reaction of diazomethane with the acid chlorides.

The only other report of these compounds found in the literature was the preparation of cyclohexanediacetic acid. Gault and Laloi reported that hydrogenation of 1,3- and 1,4-benzenediacetic acids gave the corresponding 1,3- and 1,4-cyclohexanediacetic acids, having melting points of 172 and 132°, respectively.[6] In view of the present work, it would appear that these authors inadvertently reversed the reported melting points and that hydrogenation of the 1,3-benzenediacetic acid yields a mixture of *cis*- and *trans*-1,3-cyclohexanediacetic acids.

While the Arndt–Eistert homologation reaction was satisfactory for the preparation of small quantities of these acids, other routes were sought which would be more practical for the preparation of large quantities of the *cis*- and *trans*-1,3-cyclohexanedipropionic acids (**5** and **6**). Openshaw and Robinson[7] and Leonard and Middleton[8] have reported the preparation of a number of cyclohexanone-2,6-dialkanoates by condensation of ω-haloalkanoates with 2-carbethoxycyclohexanone. These types of compounds appeared to be particularly useful reactants since it was anticipated that reduction of these keto diesters would lead to the desired isomeric 1,3-cyclohexanedialkanoic acids.

Furthermore, Stork has recently reported the extensive utility of enamines for the preparation of α-substituted ketones.[9] one particularly interesting reaction being the double addition of two moles of ethyl acrylate or acrylonitrile to the piperidine enamine of cyclohexanone, using absolute ethanol as solvent. This reaction then provides a very convenient method for the preparation of the desired keto diester (**7**).[10]

Wolff–Kishner reduction of the keto diacid (**8**) yielded a mixture of the *cis*- and *trans*-1,3-cyclohexanedipropionic acids (**5** and **6**) in approximately 65–70% yield. Careful fractional crystallization of this isomeric acid mixture resulted in the isolation of the *trans*-1,3-cyclohexanedipropionic acid (**6**) as the major product with only trace quantities of the *cis* isomer being isolated. Attempts to obtain isomer composition of the Wolff–Kishner product by gas–liquid chromatography of the dimethyl and diethyl esters failed using such columns as silicone, cyano-, benzo-, and fluorosilicones, DEGS, Carbowax, UCON-polar, and nonpolar, etc. Although it was not possible to obtain isomer composition, other data to be published later suggest that the reduction yields the *trans* acid (**6**) as the major product. Furthermore, Wolff–Kishner reduction of 2,5-cyclopentanonedipropionic acid yields pure *trans*-1,3-cyclopentanedipropionic acid.[11]



The apparent formation of the *trans*-diacid (**6**) as the major product of the reduction is of interest. The mode of formation of the keto diacid (**8**) either by the enamine or condensation reactions would suggest the configuration to be *cis*. However, until further information on the configuration of **8** is known, as well as equilibration data for *cis–trans* isomerization of **8**, any explanation for this seemingly stereospecific reduction is open to question. A detailed study of this reduction reaction is currently in progress, including the determination of the configuration of **8**, equilibration data and the effects of intermediate hydrazone formation on the course of the reduction.

For further studies of these types of disubstituted cyclic systems it was necessary to be able to identify *cis* and *trans* isomers. A useful method of identification was found to be nuclear magnetic resonance spectrometry. While these compounds did not lend themselves readily to n.m.r. studies, owing to their insolubility in suitable solvents, it was possible to observe over-all differences and to assign stereochemistry on this basis.

Qualitatively, the spectra of pairs of *cis* and *trans* isomers for all three cases (**1**, **2**; **3**, **4**; **5**, **6**) show the same differences, differences which were also noted by Finegold and Kwart[12] for the isomeric 1,3-cyclohexanediols. In the spectrum of the *cis* isomer of 1,3-cyclohexanedicarboxylic acid, peaks for the ring hydrogens are spread over a broad region, while for the *trans* isomer (**2**), because of ring inversion, the chemical shifts for hydrogens on any one carbon atom tend to assume an average value, giving in each spectrum one or more moderately sharp peaks or multiplets.

In the spectrum of *trans*-1,3-cyclohexanedicarboxylic acid (**2**) there is a quintet at 7.04 τ corresponding to the hydrogens on the 1 and 3 carbon atoms. There is a triplet at 7.63 τ assigned to the hydrogens on C-2. The multiplet splitting is 5.4 c.p.s., a value similar to that found previously[12] for the *trans*-1,3-cyclohexanediol and taken as diagnostic for that structure. An explanation was given by these workers that the averaging of *trans* and *gauche* coupling values observed was due to "strong coupling" effects. This explanation may be valid, but it appears that rapid ring inversion would average

(6) H. Gault and L. Laloi, *Compt. rend.*, **246**, 123 (1958).

(7) H. T. Openshaw and R. Robinson, *J. Chem. Soc.*, 941 (1937).

(8) N. J. Leonard and W. J. Middleton, *J. Am. Chem. Soc.*, **74**, 5114 (1952).

(9) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(10) As Stork has noted, the addition reaction to enamines is not always a straightforward process. We have been unable to effect double addition of ethyl acrylate to the enamines of cyclopentanone. In this case a high boiling material of undetermined structure is obtained. Similarly, double addition of acrylonitrile to cyclopentanone enamines gives a number of products.[11]

(11) T. L. Westman and A. E. Kober, unpublished results.

(12) H. Finegold and H. Kwart, *J. Org. Chem.*, **27**, 2361 (1962).

the observed coupling. The remaining hydrogens show one broad band at about 8.2 τ. The corresponding *cis* isomer (1) shows a series of overlapping bands in the region 7.2 to 8.7 τ, with some peaks distinguishable, although assignment is not possible. A comparison of the spectra (Fig. 1) clearly indicates distinct differences

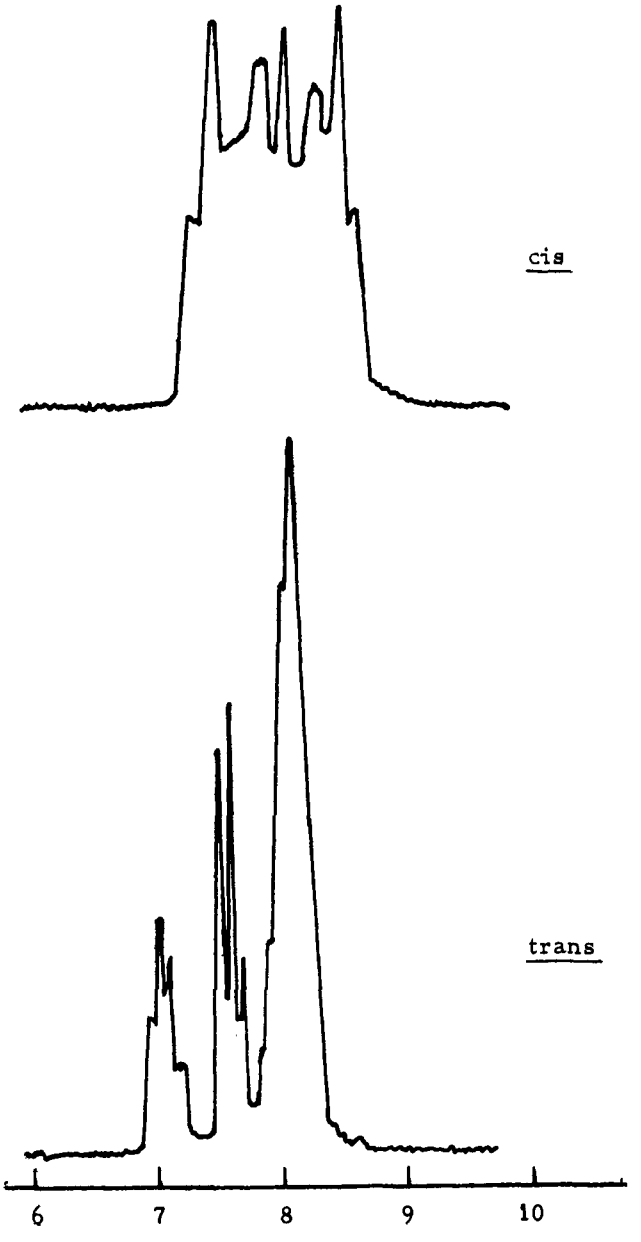


Fig. 1.—Nuclear magnetic resonance spectra of the 1,3-cyclohexanedicarboxylic acids.

in the two spectra which allow assignment of configuration.

In the spectrum of *trans*-1,3-cyclohexanediacetic acid (4) there is a single, slightly broadened peak at 7.57 τ, representing the side-chain methylene[13] and another, somewhat broader peak, centered at 8.55 τ representing all the ring hydrogens. Since an electronegative group is not directly attached to the ring, the hydrogens in positions 1, 2, and 3 no longer have distinctive chemical shifts. The corresponding *cis* isomer (3) shows a sharp side-chain methyl peak at 7.71 τ, superimposed on a series of overlapping bands extending from about 7.5 to 9.4 τ.

(13) This peak is probably wide enough to accommodate an unresolved coupling of 5 to 6 c.p.s. with the hydrogen on the adjoining ring carbon.

Located near the 7.71 τ peak there are other much weaker peaks between 7.5 and 7.6 τ, either of which may be part of a multiplet due to coupling of the side-chain methylene with the adjacent ring hydrogen. Inspection of these two spectra (Fig. 2) indicates that

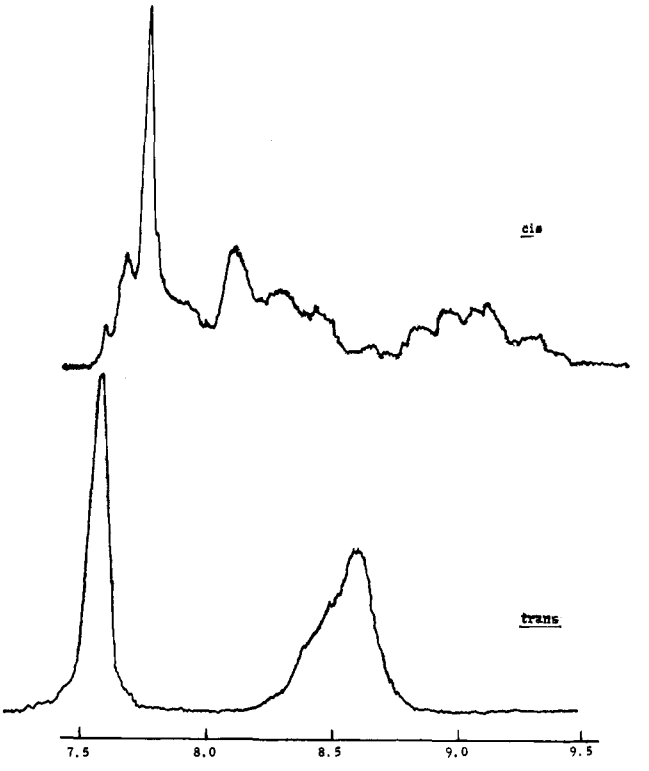


Fig. 2.—Nuclear magnetic resonance spectra of the 1,3-cyclohexanediacetic acids.

the two isomers have similar over-all patterns with respect to the *cis*- and *trans*-1,3-cyclohexanedicarboxylic acids, with the *trans* isomers displaying more defined spectra and the *cis* isomers having unresolved bands.

In the spectrum of *trans*-1,3-cyclohexanedipropionic acid (6) there is a triplet at 7.49 τ assigned to the methylene hydrogens adjacent to the carboxylic acid groups, and another multiplet, probably a triplet doubled, centered near 8.3 τ and assigned to the methylenes adjacent to the ring. There is a relatively sharp peak for the ring hydrogens near 8.6 τ. The corresponding *cis* isomer (5) shows a triplet at 7.37 τ for the methylenes adjacent to the carboxyl groups, along with a broad continuous band from about 7.7 to 9.5 τ, including one hump centered near 8.0 τ associated with methylene hydrogens next to the ring. Therefore, the 1,3-cyclohexanedipropionic acids show the same differences in their spectra (Fig. 3) as the other *cis* and *trans* isomers. It is seen that the three sets of isomers all display consistent differences between the *cis* and *trans* members, and assignment of configuration is readily made on this basis.

One point of some interest is the relatively large shift to high field found in the *cis* isomers of the *cis*-1,3-cyclohexanediacetic (3) and dipropionic acids (5) for certain of the ring hydrogens. It seems likely that this is due to the 1- and 3-hydrogens, which are principally in the axial position since the substituent groups would be expected to prefer the equatorial position

rather than the axial position suggested as preferred for the diols because of internal hydrogen bonding.[12]

Experimental[14]

cis- and *trans*-**1,3-Cyclohexanedicarboxylic Acids (1 and 2).**—The isomeric 1,3-cyclohexanedicarboxylic acids were prepared by hydrogenation of isophthalic acid using platinum oxide in acetic acid, followed by separation of isomers *via* their calcium salts[3,15]; **1**, m.p. 168–169°; **2**, m.p. 153–154°.

cis-**1,3-Cyclohexanediacetic Acid (3).**—To 40 ml. of cold, dry benzene was added 10 ml. of thionyl chloride, a few drops of pyridine, and 4.0 g. (0.023 mole) of *cis*-1,3-cyclohexanedicarboxylic acid (**1**). The mixture was allowed to stand at room temperature for 5 hr. and then heated for 1 hr. at 40°, or until the evolution of hydrogen chloride had ceased. The solvent and excess thionyl chloride were removed *in vacuo* followed by addition of 20 ml. of dry benzene and removal *in vacuo* to remove traces of thionyl chloride. The viscous acid chloride was dissolved in 100 ml. of dry ether and filtered through a glass wool plug to remove traces of solids.[16] The ether solution was then added dropwise to a stirred, cooled (ice bath) ether solution of diazomethane, prepared from 28.4 g. of N,N'-dinitroso-N,N'-dimethyltetrephthalamide (Du Pont EXR-101).[17] After the addition was completed the mixture was allowed to stand overnight at room temperature. Filtration of the mixture (to remove insoluble, flocculent material) followed by removal of the ether *in vacuo* gave the crude bisdiazo ketone as a yellow solid, m.p. 103–105° dec. The crude bisdiazo ketone was dissolved in 80 ml. of absolute methanol in a three-necked flask equipped with dropping funnel, reflux condenser with attached drying tube, and magnetic stirring bar. A solution of 0.5 g. of anhydrous silver benzoate in 6 ml. of dry triethylamine was filtered and added in portions to the stirred solution of bisdiazo ketone. Evolution of nitrogen began immediately, and after subsiding, additional silver benzoate solution was added until no further nitrogen was evolved (*ca.* 15 min.). The mixture was heated under reflux, decolorized (charcoal), filtered, and cooled. Removal of the solvent gave a pale yellow liquid which was taken up in ether, washed successively with hydrochloric acid and sodium bicarbonate solutions, dried over anhydrous sodium sulfate, and the ether removed *in vacuo*. The resultant crude dimethyl ester was hydrolyzed by refluxing with 30 ml. of ethanol containing 6 g. of potassium hydroxide. Work-up in the usual manner gave the crude *cis*-1,3-cyclohexanediacetic acid (**3**). Recrystallization from benzene–hexane (charcoal) followed by crystallization from water gave 2.5 g. (55% yield based upon 1) of the *cis*-1,3-cyclohexanediacetic acid (**3**), m.p. 138–139°.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05; neut. equiv., 100. Found: C, 59.76; H, 8.12; neut. equiv., 99.5.

trans-**1,3-Cyclohexanediacetic Acid (4).**—Using the same procedure as employed with the *cis* isomer, 4.3 g. (0.025 mole) of *trans*-1,3-cyclohexanedicarboxylic acid (**2**) was treated with 10 ml. of thionyl chloride and a few drops of pyridine. Reaction of the resultant acid chloride with ethereal diazomethane (prepared in the usual manner[18] from 28.7 g. of *p*-tolylsulfonylmethylnitrosamide), followed by homologation with silver benzoate, hydrolysis of the resultant dimethyl ester, and recrystallization from benzene–hexane and twice from water, gave 1.0 g. (25% yield based upon **2**) of *trans*-1,3-cyclohexanediacetic acid (**4**), m.p. 118–119°.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05; neut. equiv., 100. Found: C, 59.70; H, 8.10; neut. equiv., 101.

cis-**1,3-Cyclohexanedipropionic Acid (5).**—In 10 ml. of cold, dry benzene containing 3.5 ml. of thionyl chloride and a few drops of pyridine, was dissolved 1.2 g. (0.006 mole) of *cis*-diacetic acid (**3**). The resultant acid chloride was treated with diazomethane (from Diazald) in dry ether to yield the bisdiazo ketone, m.p. 95–96° dec. (from benzene–hexane). Treatment of 0.50 g. (0.002 mole) of the pure bisdiazo ketone with 0.5 g. of silver benzoate–triethylamine in methanol gave the crude dimethyl ester. Hydrolysis of the crude dimethyl ester followed by recrystallization from water gave 0.23 g. (50% yield based upon bisdiazo ketone) of *cis*-1,3-cyclohexanedipropionic acid (**5**), m.p. 97–98°.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.34; H, 9.00.

Using Du Pont EXR-101 for the diazomethane source, 13.0 g. of *cis*-diacetic acid gave 8.2 g. (55% yield based upon diacetic acid) of the *cis*-dipropionic acid.

trans-**1,3-Cyclohexanedipropionic Acid (6).**—The same procedure was employed as with the *cis* case except in this case the intermediate bisdiazo ketone could not be isolated in pure form and was used directly in the homologation step. From 1.2 g. (0.006 mole) of *trans*-cyclohexanediacetic acid (**4**) there was obtained 0.29 g. (21%) of *trans*-1,3-cyclohexanedipropionic acid (**6**), m.p. 94–95° (from water).

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.01; H, 8.94.

Cyclohexanone-2,6-dipropionic Acid (8). A.—In a typical run, 98 g. (1 mole) of cyclohexanone and 130 g. (1.5 moles) of piperidine were dissolved in 450 ml. of dry benzene, along with a small amount of *p*-toluenesulfonic acid. The mixture was refluxed overnight and the water collected in a Dean–Stark water separator. Removal of the benzene followed by distillation gave 133 g. (81%) of the piperidine enamine, b.p. 112–114° (11 mm.).

B.—The enamine from the previous experiment (132 g., 0.8 mole) was dissolved in 400 ml. of absolute ethanol, and 220 ml. (*ca.* 2 moles) of ethyl acrylate was added and the mixture refluxed for 20 hr. At the end of this time, 200 ml. of water and 10 ml. of concentrated hydrochloric acid were added and the mixture refluxed for 3 hr. The alcohol was removed by distillation, the organic material was separated, and the aqueous layer was ex-

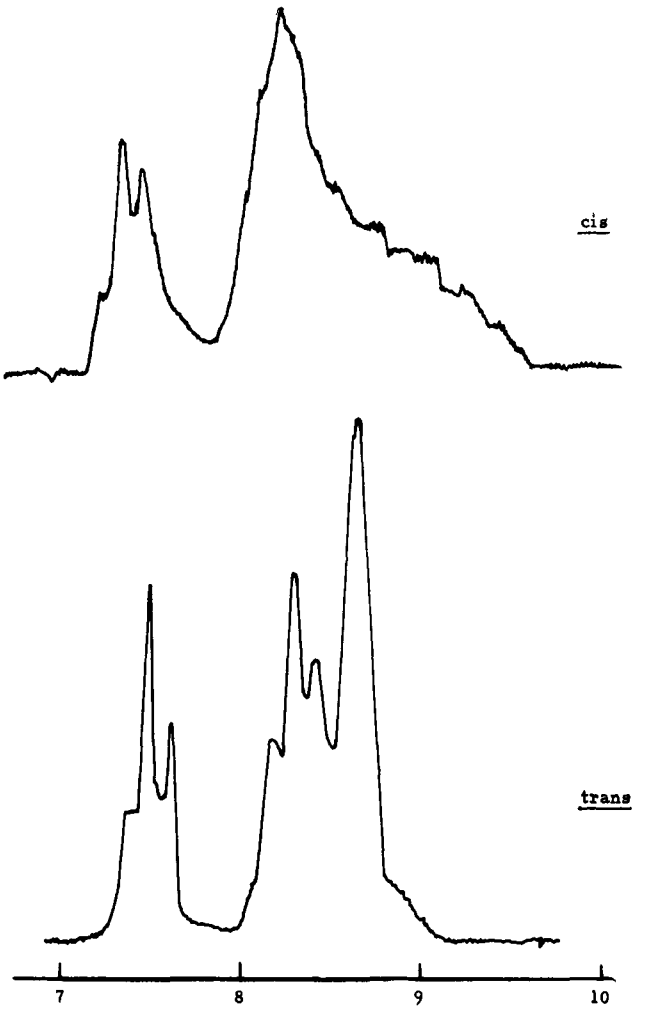


Fig. 3.—Nuclear magnetic resonance spectra of the 1,3-cyclohexanedipropionic acids.

(14) All melting and boiling points are uncorrected. N.m.r. spectra were determined in saturated pyridine solution at 56.4-Mc. frequency (tetramethylsilane as internal standard) on a Varian HR-60 spectrometer.

(15) N. L. Allinger and R. J. Curby, Jr., *J. Org. Chem.*, **26**, 933 (1961).

(16) The acid had considerable tendency to form anhydride under a variety of conditions tried.

(17) The diazomethane was generated following the procedure used for N-nitrosomethylurea: F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(18) Th. J. de. Boer and H. J. Backer, *Rec. trav. chim.*, **73**, 229 (1954).

tracted with 70 ml. of ether. After drying the combined organic solution over anhydrous magnesium sulfate, the ether was removed *in vacuo* and the residue distilled at 3 mm. pressure until the pot temperature reached 180°. Upon cooling, the residue solidified to yield the crude diethyl ester of cyclohexanone-2,6-dipropionic acid. This ester was recrystallized by dissolving in 50% ethanol, warming to *ca.* 50° and adding water until cloudy. After two recrystallizations, the diethyl cyclohexanone-2,6-dipropionate had m.p. 63–64°; yield, 145 g. (60%).

C.—The cyclohexanone-2,6-dipropionic acid (**8**) was prepared from the diethyl ester by refluxing with excess concentrated hydrochloric acid for 2 hr. Work-up in the usual manner gave the product acid (**8**) from water, m.p. 144–145° (lit.[3] m.p. 145°).

Wolff–Kishner Reduction of Cyclohexanone-2,6-dipropionic Acid.—In a 500-ml. three-necked flask equipped with a mechanical stirrer, thermometer, and reflux condenser was placed 21 g. (0.37 mole) of potassium hydroxide and 150 ml. of diethylene glycol. After stirring, with gentle heating, for 1 hr. the potassium hydroxide had dissolved. To the stirred warm solution there was added 18 g. (0.075 mole) of the keto diacid (**8**) and 5 ml. of 97% hydrazine. After heating for 2 hr. at 100–110° with stirring, the condenser was removed and heating was continued until the temperature had reached 180–190°. After heating for an additional 4 hr. the evolution of nitrogen had ceased and the reaction mixture was poured into 250 ml. of water. After acidification with hydrochloric acid the mixture was extracted with ether. The ethereal solution was extracted with saturated sodium bicarbonate solution, the bicarbonate extracts decolorized with charcoal, acidified with concentrated hydrochloric acid, and extracted with ether. After drying over anhydrous sodium sulfate the ether was removed *in vacuo* to yield a viscous oil which solidified to a white solid after standing overnight in the refrigerator. The yield of the mixed *cis*- and *trans*-dipropionic acids was *ca.* 12 g. (71%). Approximately 4 g. of the crude mixed acid material was added to water and heated to 50° at which temperature the acid began to oil and additional water was added until the total volume was 400 ml. The clear aqueous phase was separated from the residual oil while still hot. After cooling, the aqueous solution deposited *ca.* 1 g. of the crude *trans* acid (**6**) which, after four recrystallizations, had m.p. 94–95°. A mixture melting point of this material with the *trans*-dipropionic acid (**6**) obtained from the Arndt–Eistert reaction was undepressed and their infrared spectra were identical except for band intensities. Upon further standing, the aqueous solution deposited in very low yield, the *cis*-dipropionic acid (**5**) which, after three recrystallizations, had m.p. 97–98°. This acid had an infrared spectrum identical with the *cis*-dipropionic acid (**5**) obtained from the Arndt–Eistert reaction and a mixture melting point of the two acids was undepressed. A mixture melting point with the *trans*-dipropionic acid (**6**) was 77–81°.

The Addition of Amines to Carbohydrate α-Nitroolefins

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June 3, 1963

The addition of some aliphatic and aromatic amines to D-*arabino*-3,4,5,6-tetraacetoxy-1-nitro-1-hexene in anhydrous methanol and some reactions of the resulting products are described. The addition of aniline yields two crystalline isomers both of which are converted to 3,4,5,6-tetra-*O*-acetyl-2-(*N*-phenylimino)-D-*arabino*-hexulosonitrile (VII) by treatment with acetic anhydride in pyridine.

The preparation of carbohydrate α-nitroolefins is well known.[2] Recently, O'Neill[3] and Sowden[4,5] have reported the addition of ammonia and methanol to D-*arabino*-3,4,5,6-tetraacetoxy-1-nitro-1-hexene (I). Sowden obtained an epimeric pair of 2-acetamido-1,2-dideoxy-1-nitro-D-hexitols which were converted to D-mannosamine and D-glucosamine hydrochlorides *via* the Nef reaction.[6] The addition of amines to I, therefore, seemed a likely route to some interesting N-substituted amino derivatives of D-glucose and D-mannose.

Addition of one equivalent of *p*-toluidine, benzylamine, cycloheptylamine, cyclohexylamine, ethanolamine, and isopropylamine to a solution of I in anhydrous methanol gave, in each case, only one of the two possible isomers in crystalline form. The yields and some physical constants of the adducts are reported in Table I.

The addition of aniline yielded both isomers in crystalline form. The higher melting 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1-nitro-2-(*N*-phenylamino)-D-hexitol (V) was obtained in 28% yield, and the lower melting isomer in 44% yield. Sowden and Oftedahl[4] found that the addition of ammonia to nitroolefin gave *O*-deacetylated-*N*-acetylated derivatives. However, all the amine–nitroolefin adducts isolated in this study were fully *O*-acetylated. De-*O*-acetylation probably did not occur because only one equivalent of the amines was employed. Probably O → N acetyl migration did not take place because of the blocking effects of the alkyl and aryl groups attached to the amino groups. No such migration was observed in the case of the aromatic amines during reaction times (overnight) comparable to those used in the ammonia addition. The aliphatic amine adducts were isolated after 30 min. as they decomposed overnight giving brown solutions.

The absence of a band at 1600 cm.$^{-1}$ in the infrared spectra of the aniline and cyclohexylamine adducts proved that they are true addition products. The band was present in the spectrum of the nitroolefin and is characteristic of double bonds.[7] As mentioned before, the aliphatic amine adducts are unstable at room temperature, but the solids may be kept for several weeks at −10° without decomposition. The crystalline aromatic adducts are stable at room temperature. An attempt to stabilize the cycloheptylamine adduct by acetylation to the amide with acetic anhydride was unsuccessful, and nitroolefin was isolated in 80% yield. Acetic anhydride was without action on the higher-melting aniline adduct. Treatment of this adduct with acetic anhydride in pyridine gave a totally unexpected product which will be discussed later.

Hydrogenation of the amine–nitroolefin adducts in

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